Journal of Surgical Oncology 1998;68:255–267

REVIEW ARTICLE

Laparoscopic Colectomy for Colon Cancer: Trial Update

LUCA STOCCHI, MD, AND HEIDI NELSON, MD, FACS*
Division of Colon and Rectal Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Laparoscopic colon surgery is gaining acceptance for benign conditions, but cannot yet be considered an established procedure for malignancy. The main reported benefit of the technique is the reduction in length of hospital stay. Other potential benefits such as cosmesis, improvement in quality of life, physiologic and immunologic advantages, as well as reduced complication rates have not been clearly demonstrated. Concerns about laparoscopic colon surgery for cancer including the possibility of inadequate resection, tumor staging, and altered tumor spread due to pneumoperitoneum have only been partially addressed by retrospective and experimental studies and require a prospective randomized trial for definitive resolution. Details of the trial currently underway sponsored by the National Institutes of Health are described. Although innovations in clinical practice and increased familiarity account for the expanding popularity of laparoscopic colon surgery, results from this and similar worldwide trials are needed before this approach can be recommended for cancer.
J. Surg. Oncol. 1998;68:255–267.

KEY WORDS: **laparoscopy; colorectal neoplasm; length of hospital stay; surgical complications; learning curve**

INTRODUCTION

Although practiced by gynecologists for years, laparoscopy has recently generated revolutionary changes in surgery. Soon after its introduction, laparoscopic cholecystectomy became the standard of care as a result of patient- as well as cost-related benefits; consequently, almost every field of surgery has been challenged by this innovative modality, colon and rectal surgery being no exception. In fact, like laparoscopic cholecystectomy, patient-related benefits have been demonstrated repeatedly for laparoscopic colon surgery, including reductions in intraoperative blood loss, postoperative pain, length of postoperative ileus, and most of all, length of hospital stay with faster complete recovery. Unlike laparoscopic cholecystectomy, laparoscopic colon and rectal surgery has not been unanimously accepted. This principally relates to the fact that cancer represents a major indication for colorectal surgery and several oncologic concerns pertinent to laparoscopic surgery have yet to be adequately addressed. Whether laparoscopic techniques accomplish proper oncologic resection and staging and whether pneumoperitoneum alters patterns of recurrence are concerns that have become the subject of considerable scrutiny.

Although several recent investigators have described favorable experiences with laparoscopic cancer surgery, an issue of such magnitude demands a large prospective randomized trial, one that can provide the statistical power to definitively resolve the issue. The following review therefore describes the potential benefits and risks associated with oncologic laparoscopic colorectal surgery; the reasons that render prospective randomized trials scientifically necessary and ethically justified; and the

Grant sponsor: Ethicon (L.S.).
*Correspondence to: Heidi Nelson, MD, Division of Colon and Rectal Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Fax No.: (507) 284-1794. E-mail: nelsonh@mayo.edu
Accepted 19 May 1998

design and update of the trial sponsored by the National Institutes of Health (NIH) and other international trials. Finally, recent changes in the approach and practice of laparoscopic colorectal surgery which could further ignite interest for this ongoing study are delineated.

BENEFITS

Laparoscopic colon resection theoretically should achieve benefits analogous to those demonstrated for laparoscopic cholecystectomy, i.e., reduction in size of incisions, postoperative pain, narcotic usage, length of hospital stay (LOS), and overall costs. However, there are a number of factors that make the laparoscopic approach to the colon notably different. While the gallbladder is a fixed organ, the colon often requires extensive mobilization involving multiple abdominal quadrants to facilitate exteriorization and resection. Moreover, colonic resection poses several technical challenges, including the necessity to ligate major blood vessels, perform an anastomosis, and remove a large bulky specimen. Analysis of the procedure, therefore, requires an adjustment for the long learning curve, influenced by the complexity of the procedure. Further, because of the diversity of the procedures (right vs. sigmoid colectomy or stoma formation) and disease processes (polyps vs. diverticulitis), most series to date are small, heterogeneous, and uncontrolled, which makes an accurate evaluation of the results difficult. According to these important variables, the exact extent of benefits is, at present, not clear. Despite this, emerging evidence supports that at least some advantages can be confirmed repeatedly and therefore can be considered real, while others are less consistent, more controversial, and therefore best regarded as potential.

Reported Benefits

Reduction of LOS. The reason for a shorter postoperative ileus remains elusive and in fact is likely multifactorial. Lesser surgical trauma or perhaps less extensive manipulation of the bowel could result in less pain as well as reduced intestinal edema and subsequent ileus. In humans, additional factors such as decreased pain with reduced narcotic usage, earlier ambulation and oral intake, and more generally, a more rapid restoration to a sense of well-being have been considered. Regardless of the physiologic mechanisms involved, a reduction in LOS after laparoscopic vs. open colorectal surgery has repeatedly been reported. Preliminary results of the Laparoscopic Bowel Surgery Registry, including 1,056 patients reported by 118 surgeons, indicate a statistically significant reduction of postoperative stay when laparoscopically completed patients are compared to converted ones (5.6 vs. 8.4 days) [1]. At least 12 other studies have documented a reduction in LOS for patients undergoing laparoscopic vs. open colorectal surgery. Differences between open and laparoscopic colon resection vary from 2 to 5.3 days, with LOS associated with laparoscopic colon resection ranging from 3.6 to 7.8 days vs. LOS associated with open surgery ranging from 8 to 15.2 days [2–13]. However, these results have been challenged on the basis that they may be biased by patient selection, psychological conditioning of the patient (anticipation bias), and earlier feeding.

Psychological conditioning of the patient, derived from higher expectations from laparoscopic colectomy or different anticipations and treatments from both medical and non-medical personnel, has been proposed as playing a role in achieving reduced lengths of ileus [14]. As much as this may be true, it is difficult in human studies to ‘‘blind’’ the participants and treating physicians to avoid such biases. For more objective data, therefore, animal data must be relied upon. In fact, a number of animal models have not supported the role of psychological conditioning as a valid explanation [15–17]. In a study of 39 dogs equally assigned to laparoscopic, laparoscopic-assisted, and open colectomy, a more rapid return to normal gastrointestinal transit was shown for both laparoscopic groups compared to open surgery despite identical postoperative management [18]. In general, animal studies have repeatedly shown a shorter postoperative ileus in experimental models where conditioning is unlikely to play a major role.

Earlier feeding has also been implicated. It is claimed that earlier feeding can reduce LOS after open cases in the same manner as after laparoscopic colectomy, if adopted in a systematic and aggressive fashion [19]. However, the impact of earlier feeding per se is also questionable. In an attempt to challenge laparoscopic surgery results, 35 patients undergoing minilaparotomy were compared to 42 who were treated with laparoscopic resection with a similarly aggressive postoperative diet progression. Despite similar postoperative management, postoperative discharge was significantly shorter after laparoscopic vs. open surgery (5.4 vs. 6.9 days, $P = 0.014$) [20]. In all, decreased LOS after earlier feeding in the absence of minimally invasive technique has not been confirmed consistently [21].

Although selection bias cannot be altogether avoided and might be contributory to the favorable effect with laparoscopy, the reproducible reduction in LOS suggests true and real benefits and as such this should be considered an achievement of the laparoscopic approach.

Potential Benefits

Potential advantages that have been attributed to laparoscopic colorectal surgery include minimal skin incision, improvement in the quality of life, cost-containment (at least at the same level as open surgery), and physiologic and immunologic benefits that could result in reduced rates of complications.

TABLE I. Analysis of Costs for Laparoscopic vs. Open or Converted Colectomy

Reference	Year	No. patients (laparoscopic/open)	Types of procedure	Costs ($)		
				Open	Laparoscopic	Converted
Falk et al. [2][a]	1993	34/−	Sigmoid colectomy	13,000	12,500	15,000
			Right colectomy	11,000	12,500	18,000
Senagore et al. [4]	1993	38/102	Colon and rectal	14,449	12,131	17,583
Hoffman et al. [5]	1994	80/53	Colon and rectal	10,213	12,464	13,956
Musser et al. [6]	1994	18/24	Colon and rectal	11,207	9,811	−
Van Ye et al. [56]	1994	14/20	Colon and rectal	18,200	18,300	−
Pfeifer et al. [22]	1995	53/53	Colon and rectal	26,903	29,626	19,702
Fine et al. [67]	1995	30/−	Colon and rectal	13,050	11,010	−
Tucker et al. [35]	1995	37/−	Colon and rectal	14,000	9,200	16,000
Liberman et al. [11]	1996	14/14	Sigmoid colectomy	13,400	11,500	−
Philipson et al. [68]	1997	28/33	Right colectomy	7,881[b]	9,064[b]	−

[a]Values are estimated from their figure 6.
[b]Estimate in Australian dollars.

Cosmesis. There is no doubt that cosmetic benefits can be realized by the application of minimally invasive colorectal techniques; such benefits in some conditions may make laparoscopic colonic resection a patient-driven procedure, similar to what has been seen for laparoscopic cholecystectomy. Arguing against this, however, elderly patients are usually operated on for colorectal cancer and cosmesis is not as important as a safe recovery and an appropriate oncologic procedure. A patient survey investigating the importance of cosmesis in colorectal surgery suggests that laparoscopic surgery is not considered a substantial esthetic advantage when compared to open procedures [22].

Cost-effectiveness and quality of life. Other more controversial benefits are being studied which regard cost-effectiveness and quality of life issues. It is generally accepted that laparoscopic colorectal procedures are more complex and require longer operative times as well as the use of at least some disposable equipment. Thus, overall operating room costs are typically higher for laparoscopic surgery. Conversely, reductions in hospital costs and improvements in quality of life should derive from faster return of bowel function, more limited use of analgesic medications, reduced LOS, and reduced rates of late complications. Whether or not laparoscopic colorectal surgery is cost-effective depends on the balance of these two opposing sets of factors: those that increase operating room costs and those that decrease overall hospital costs. No doubt costs are also influenced by the learning of the procedure. According to data reported thus far, costs for laparoscopic and open surgery tend to be very similar, and appear to be practice dependent (Table I) [2,4–6,11,22,35,56,67,68].

Although some studies have been able to show a reduction in cost already apparent at the time of discharge, in many cases the real advantages of laparoscopic colectomy can only be appreciated when costs are analyzed in a more comprehensive way, i.e., when time required to return to an active life is considered [20]. From a practical standpoint, time to return to work can be measured and economic impacts calculated for those who are employed, even though there will be variations according to the type of job and personal motivations associated with each patient. The value of the return of a non-employed person to his/her usual activities is more difficult to quantitate and has not been carefully evaluated. Therefore, apart from the crude LOS, the benefits of laparoscopic compared to open surgery should be tested by the ability of patients to return more quickly to their daily activities, including work. Since this issue is vital to the definitive success of laparoscopic surgery, it has been included as an outcome in the national trial.

Physiologic and immunologic benefits. Several studies have focused on the physiologic and immunologic effects of minimally invasive surgery, specifically the effects of pneumoperitoneum. Although laparoscopic surgery alters cardiovascular and respiratory performance, as evident by the alterations in several parameters, including blood pressure, cardiac index, systemic vascular resistance, $PaCO_2$, and pH, initial concerns regarding possible harmful effects due to excessive CO_2 absorption have never been proved definitively in either animal or clinical settings. In fact, the reverse is true: laparoscopy produces less disturbance in pulmonary function [23]. Moreover, the lack of a formal incision and celiotomy has prompted many to investigate whether laparoscopic techniques can improve other parameters of postoperative recovery, including recovery of immunologic defenses.

Some reports have suggested reduced levels of immunosuppression from surgical trauma following laparoscopy compared to open surgery, using a variety of immune response indicators. For example, there is evidence that levels of interleukin 6 (IL-6), considered a marker of stress and a predictive factor for postoperative complications, are decreased after laparoscopic vs. open colec-

tomy [24]. Other animal studies have demonstrated improved preservation of delayed-type hypersensitivity reactions when smaller incisions were used [25]. At variance with this, a small prospective randomized trial of laparoscopic vs. open colon resection for adenocarcinoma has found an increased level of IL-6 and C-reactive protein (CRP) in the laparoscopic group [26]. In another study, levels of IL-6 have been found to be dependent on the operative time, rather than the technical approach used [27]. Therefore, at present the theoretical benefits of reduced surgical stress and its possible impact on immunity, septic complications, and tumor recurrences after cancer surgery still require clarification and confirmation.

Surgical complications. Assuming laparoscopy to be a less invasive approach, some investigators have anticipated reduced rates of complications, specifically complications related to wounds such as infections and adhesions. In fact, early reports suggested that laparoscopy in colorectal surgery might be associated with fewer postoperative infections, with rates of 3.6% and 1.2% for laparoscopic and 7.9% and 12.7% for open surgery reported in 2 series [28,29]. Unfortunately, other series have not confirmed benefits with respect to overall morbidity or mortality for laparoscopic surgery. Reviewing 5 reported series considering more than 500 patients, mortality rates range from 0 to 2.6%, averaging approximately 1% or less, and morbidity rates range from 11% to 25% [2,5,12,29,30]. The specific contribution of laparoscopy to morbidity is difficult to quantify, but at least one investigator reported a 14% incidence of laparoscopic-related complications [31]. It is presumed that laparoscopic-specific complications are likely to be more common early rather than late in the learning curve experience. In general, rates of morbidity and mortality are very comparable to those reported for open surgery for at least short-term perioperative complications [1,4,6,9,10,20, 30,32–38].

Whether long-time advantages can be gained, such as the reduction of small bowel obstruction from a reduced incidence of postoperative adhesions, as suggested by animal and human studies, cannot yet be confirmed. Animal studies have demonstrated a reduced risk of adhesions following laparoscopic surgery compared to open laparotomy [17]. The same effects have been noted for laparoscopic appendectomy where subsequent evaluations documented significant reductions for laparoscopic vs. open appendectomy. In a randomized study of 40 patients, a ‘‘second look’’ laparoscopy, performed 3 months after the primary procedure, revealed the presence of significant adhesions in 80% of patients treated with laparotomy compared to 10% in the laparoscopic group [39].

CURRENT CONTROVERSIES

As with all new technologies, the potential for benefits must be balanced against the potential for new or unique risks. For benign conditions, in experienced surgical hands there appears to be no significant downside to the application of laparoscopic surgery in properly selected cases. The same is not true for laparoscopic colorectal cancer surgery. The potential risks of the application of laparoscopic colectomy for cancer include the possibility that inadequate resection will be performed, leading to the possibility of insufficient bowel or radial margins. Further, it is conceivable that laparoscopy does not accomplish the same degree of lymphovascular and hepatic staging and/or it may alter patterns of tumor dissemination, specifically due to factors related to the insufflation of intra-abdominal CO_2.

Inadequate Resection

At least on a theoretical basis, the possibility exists that minimally invasive techniques may not provide the same extent of oncologic resection as that accomplished using standard open surgery. Cutting corners for technical difficulties could lead to inadequate clearance of the bowel, lymphovascular structures, and radial margins. Fortunately, current data suggest that the same bowel resection can be accomplished with laparoscopic surgery as for open surgery. A number of investigators have demonstrated that the same lymph node harvest is accomplished with both techniques (Table II) [5,6,8,9,10,12,26, 35,56,67,69]. Early results from a large prospective randomized trial, which has accrued a total of 408 patients, demonstrate that total length as well as proximal and distal bowel margin lengths and lymph node sampling are the same for open and laparoscopic surgery. Regarding radial clearance of locally advanced tumors such as advanced T3 or T4 lesions, it is not clear yet whether radical resections with wide tumor clearance can be achieved with laparoscopic surgery, since most investigators have not included such tumors in their laparoscopic experience.

A final issue concerns the possibility of the removal of the wrong portion of bowel, i.e., the portion not containing the pathology. Fortunately, this has only rarely been reported [40]. Early on in the experience with laparoscopic colorectal surgery a number of authors acknowledged the difficulty associated with identifying the specific site of pathology due to the inability to perform intraoperative palpation. Early recognition of this problem allowed laparoscopic surgeons to adapt their practice. Currently, bowel pathology is confidently localized prior to surgery, thus avoiding this problem altogether.

Staging Limitations

Even though the extent of the resection appears to be the same for laparoscopic as for open surgery, this does

TABLE II. Lymph Node Retrieval for Open vs. Laparoscopic Colorectal Surgery

Reference	Year	No. patients (laparoscopic open)	Type of operation	Laparoscopic (ranges, when reported)	Open
Hoffman et al. [5]	1994	32/31	Colon and rectal	8.0	6.1
Musser et al. [6]	1994	17/24	Colon and rectal	10.6	7.9
Van Ye et al. [56]	1994	14/20	Colon and rectal	10.5 (0–32)	7.6 (2–19)
Fine et al. [67]	1995	30/−	Colon and rectal	8.7–10[b]	10[b]
Tucker et al. [35]	1995	20/15[a]	Colon and rectal	8.7	6.4[a]
Saba et al. [8]	1995	20/25	Segmental colectomies	6 (0–21)	10 (2–27)
Franklin et al. [9]	1996	192/214	Colon and rectal	37	32
Gellman et al. [10]	1996	37/38	Colon and rectal	9.3	9.5
Lord et al. [12]	1996	13/19	Right colectomy	11.6	10.1
		19/30	Anterior resection	7.8	8.9
Moore et al. [69]	1996	30/34	Right colectomy	16.9 (4–56)	15.9 (4–30)
Stage et al. [26]	1997	15/14	Colon and rectal	7[c] (3–14)	8[c] (4–15)

[a]Comparison with patients converted to open procedures.
[b]Three different surgeons are reported and compared to ''average for similar cases.''
[c]Median.

not insure that the same comprehensive staging evaluation is performed with the new technique. It has been described that the same number of lymph nodes can be sampled, providing a reasonable level of confidence that at least regional staging is accurate and equivalent. There is less certainty regarding the ability to thoroughly evaluate the abdominal cavity and the liver. There is no doubt that the laparoscope gives good visualization of the peritoneal cavity, but that minimally invasive surgery is limited with respect to the ability to perform palpation. In this regard, hepatic lesions on the liver surface are rather well demonstrated by laparoscopy, but deeper, parenchymal tumors remain undetected. At present, the combination of computed tomographic (CT) scanning and laparoscopic inspection is considered complementary and likely to be as accurate as intraoperative bimanual palpation. However, this remains to be demonstrated in a more controlled trial fashion. In the future, it is anticipated that newer staging modalities such as laparoscopic ultrasonography will be useful. In open surgery it is well recognized that intraoperative ultrasonography is the most accurate staging modality. Whether laparoscopic ultrasound probes can produce the same degree of accuracy has yet to be widely demonstrated.

Altered Tumor Spread

The most ominous concern raised to date regards the possibility that the use of a pneumoperitoneum alters the pattern of distribution of intra-abdominal tumor cells. Early anecdotal reports and subsequent clinical series reported alarming rates of wound or trocar site tumor recurrences. Not only were such recurrences present at the site of tumor extraction, but as well in the site where cannulas had been used to perform the resection. Since similar findings had been described for other intra-abdominal malignancies including pancreatic, ovarian, and gallbladder cancer [41], it was not clear whether these types of recurrences were an inevitable consequence of the minimally invasive techniques or perhaps related to a learning experience. A review of the reported rates of wound tumor recurrence following laparoscopic colorectal surgery (Table III) [9,10,31,32,37,38,42,48,58,70,72,73] highlights several points regarding this issue. It is clear that in some earlier studies the incidence of wound tumor implants far exceeded that reported for open surgery. Berends and colleagues [42], e.g., described a rate of 21%, which greatly exceeds the expected rate for open surgery (0.6–2.5%) [43–45]. It is also evident that some investigators with large experiences, totaling >100 patients in single-institution series and >400 patients in multi-institution series, can achieve rates of between 0 and 2.4%. A definitive analysis of this problem will only come at the conclusion of large prospective randomized trials, those trials statistically powered to confidently resolve this issue definitively. However, for at least a current analysis, it appears that the incidence of trocar site recurrence seems to be reducing, at least suggesting that the learning curve may have influenced this adverse outcome in the same way as the learning curve influenced the rate of common bile duct injuries for laparoscopic cholecystectomy. Fortunately, data at present suggest that wound tumor implants are not an inevitable consequence of laparoscopic techniques. Cautious evaluation is still advised, however.

A number of investigators have used laboratory models to better understand the possible contribution of laparoscopy to wound tumor implants, with the goal of reducing or eliminating the risk of such recurrences. It is well recognized that free-floating viable exfoliated tumor cells are present within the abdominal cavity at the time of surgery [46]. It also has been demonstrated that such cells can be concentrated or focused at sites where cannulas are introduced and instruments frequently manipulated [47]. It is conceivable that a leaking trocar would

TABLE III. Reported Rates of Wound Tumor Recurrences Following Laparoscopic Colorectal Surgery

Reference	Year	No. wound recurrences/ No. patients	%
Guillou et al. [32]	1993	1/57	1.8
Berends et al. [42]	1994	3/14	21
Drouard et al. [70]	1995	12/507[a]	2.4
Boulez [58]	1996	3/117	2.5
Fleshman et al. [48] (COST group)	1996	4/372	1.1
Franklin et al. [9]	1996	0/192	0
Gellman et al. [10]	1996	1[b]/58	1.7
Hoffman et al. [71]	1996	1/130	0.8
Kwok et al. [37]	1996	1[b]/83	1.2
Vukasin et al. [73]	1996	5/451	1.1
Lacy et al. [72]	1997	0/106	0
Larach et al. [31]	1997	0/108	0
Fielding et al. [38]	1997	2[c]/149	1.3

[a]Five cases of metastatic disease or carcinomatosis.
[b]After palliative procedure.
[c]After one palliative procedure.

allow for the focus of viable intra-abdominal tumor cells, accumulating an inoculum sufficient to support tumor growth. Since tumor growth is typically dependent on a minimum size inoculum, any measures that can reduce the size of tumor inoculums would be likely to reduce the risk of trocar site recurrences. Therefore, reducing the leaking of CO_2 around cannulas, protecting wounds at the time of tumor extraction, and irrigating wounds to simply reduce the number of tumor cells present are all likely to be effective for the prevention of this clinically disastrous problem.

Other possible effects of laparoscopy on tumor growth are less well defined. Fortunately, there is nothing to date that indicates that patients would be more susceptible to liver or lung metastases through the use of a pneumoperitoneum, i.e., the transperitoneal absorption of viable tumor cells that could spread through the general circulation.

Clinical Studies

Although the incidence of trocar site recurrence has been investigated in human studies, and a number of animal studies have been performed to evaluate the ultimate impact of laparoscopy on cancer outcomes, scant data are available on the most significant factor, i.e., survival following cancer surgery. Only a few reports to date have included survival data. In a series of 192 patients undergoing laparoscopic compared to 224 patients undergoing open colon surgery, Franklin and colleagues [9] described results for overall and disease-free survival for patients with stage I–IV colon cancers. For curable cancers (stages I–III), the percent of patients alive without evidence of disease was very comparable for laparoscopic vs. open surgery (85% vs. 80%). For patients with stage IV cancer, the number that was alive with disease was also comparable for laparoscopic and open surgery (58% vs. 75%, respectively) [9].

Survival data are also available from the Clinical Outcome of Surgical Therapy (COST) Study Group, the surgical consortium that is undertaking the large national prospective randomized trial. Sixteen surgeons contributed a total of 372 patients to the survey evaluation, reporting not only on trocar site recurrences, as described above, but also on regional and distant recurrences and overall survival. According to the stage-dependent survival curves, these results do not appear to differ from those reported for the overall population based on data following standard open resection [48]. These data do not support the widespread application of laparoscopic cancer resection, rather they indicate that it is ethical and reasonable to proceed with large controlled trials, trials that will be large enough to answer the key cancer questions.

RATIONALE FOR A PROSPECTIVE RANDOMIZED TRIAL

Although results from the studies discussed are reassuring, less than optimal sample sizes as well as limited follow-up do not allow resolution of the most important controversies regarding the oncological risks associated with laparoscopic colon surgery. Therefore, at present, laparoscopic colectomy for cancer cannot be recommended outside the setting of clinical trials [49]. The need for a clinical trial on laparoscopic colon cancer surgery is heightened by the fact that the extent of the benefits and risks has not been clearly delineated. There is clearly a suggestion from previous studies that patient-related benefits can be realized but also that cancer risks may be incurred. Only properly designed studies of sufficient size to detect small but clinically relevant differences in outcomes will be conclusive. In addition, such trials need to be prospective and allocate patients in a random fashion to avoid selection bias. Although cancer outcome will be pivotal to decide the fate of laparoscopic colon surgery, a number of other issues including quality of life and costs will be important to the widespread acceptance of laparoscopic colectomy assuming the oncologic results are equivalent.

DESIGN OF THE NIH TRIAL (http://ncctg.mayo.edu/lapcolon

The NIH trial proposes to study 1,200 patients, randomly assigned to undergo laparoscopic or open colectomy for curable colon cancer and followed for a period of up to 8 years [50]. The primary aim of the study is to examine differences between open and laparoscopic colon surgery for cancer with respect to disease-free and overall survival. Secondary aims of the trial will assess the frequency of early and late morbidities and postop-

erative mortality. Additional aims will focus on differences in quality of life as well as costs and cost-effectiveness between the two arms.

Eligibility and Stratification

Patient eligibility requires that the patients be consenting adults over the age of 18 years and have a clinical diagnosis of a right, left, or sigmoid primary adenocarcinoma. The diagnosis requires confirmation by physical examination, sigmoidoscopy, barium enema, or colonoscopy. Patients are stratified at the time of randomization according to the site of the primary tumor, the treating institution, and the American Society of Anesthesiology (ASA) classification (I–II vs. III) [51].

Exclusion Criteria

Exclusion criteria include pregnancy and synchronous or previous malignancies (except for superficial non-melanomatous skin cancer and *in situ* cancer of the cervix). Patients will also be excluded if they have associated gastrointestinal conditions that require more extensive surgery, such as ulcerative colitis, Crohn disease, or familial adenomatous polyposis. It is intended that patients will undergo segmental resection alone, rather than more extensive abdominal surgery, to provide a homogeneous population of patients and procedures. Similarly, bulky or locally advanced tumors (T4 lesions), or the presence of perforating or obstructing disease requiring urgent operation, are not considered eligible for technical and cancer considerations. Since the focus of the trial is on curative resection of average-risk patients, metastatic disease (stage IV) or an ASA IV or V classification are also contraindications to enrollment. At the surgeon's discretion prior to randomization, patients can be declined participation in the trial if they are known to have extensive scars and adhesions from previous surgery. Otherwise, all patients, regardless of previous surgery, will be randomly assigned to undergo either laparoscopic or open surgery. Finally, transverse colon cancers and rectal cancers are not eligible for the trial for technical as well as for cancer-related reasons. It is anticipated that future trials will examine the same issues in rectal cancers, with emphasis on the issue of local recurrence, which is highly variable according to surgical technique. This would represent an objective quite different from a study on laparoscopic colon surgery, where the impact of surgery on local recurrence rate for colon cancer is not as important as for rectal cancer.

Statistical Analysis

Statistical analysis will be conducted anticipating a conversion rate of 20% and an equal distribution between high-risk stage II–III and early diseases. Assuming these hypotheses are respected, the statistical design specifies that there is a 10% chance that laparoscopic colectomy will be considered less effective than open surgery when the two treatments are actually equivalent. On the other hand, the probability of concluding equivalence ranges from 19% in case of a 5% absolute decrease in the 3-year recurrence rate for laparoscopic colectomy to 0.2% if such a difference is 10%. In other words, a clinically significant difference will likely not be underestimated because of the statistical design. However, it is important to point out that the sample size has been designed to test whether the two treatments are equal. Therefore, if laparoscopic colectomy were slightly superior it might not be possible to detect it based on this study.

Quality of Life

An important and relatively new issue addressed by the trial is the measurement of quality of life. Quality of life following colectomy has not been frequently analyzed in the literature and accurate and objective estimations have been difficult to attain. Therefore, quality of life is being studied from three complementary points of view: patient self-reported symptoms, patient self-reported functional status, and a more objective measurement scale of compliance to treatment referred to as Q-TWiST (quality-adjusted time without symptoms of disease and toxicity of treatment). The Q-TWiST value will be calculated by considering 5 basic health states: the perioperative period, adjuvant chemotherapy, time without symptoms and toxicity, late complications, and relapse. Then, time spent in each state will be noted and multiplied by a coefficient based on quality of life reported by patients in that health state. Lastly, the adjusted periods will be summed to obtain the final single value, which will allow comparisons among patients with different follow-up.

Costs

Costs incurred for laparoscopic surgery are known to be highly influenced by surgical practices as well as economic differences reflected by local cost of living factors. Therefore, costs cannot be simply evaluated by considering charges in one or two institutions. Such a limited view would likely reflect the economic differences in local or regional environment more than the impact of laparoscopic surgery as a whole. Therefore, costs are being analyzed both from a resource utilization standpoint and from a hospital charges standpoint, analyzing multiple and diverse institutions. Resource utilization studies include such items as LOS, intensive care unit stay, operative times, anesthesia times, and disposable laparoscopic equipment utilization, which will allow more generalized application of cost information to different medical models, i.e., local factors such as personnel wages vs. space-use costs can be accounted for. Costs

will also be reported according to total hospital charges, i.e., the billing received by the patient. Since multiple institutions are participating, and these institutions represent diverse regional location and diverse practice types, this should broadly reflect between national experience for laparoscopic vs. open surgery costs.

At the conclusion of the trial, costs and quality of life will be simultaneously evaluated to report quality-adjusted survival, i.e., the expense necessary for each quality-adjusted year of life gained. The present limits range from $100,000, which would be considered cost-ineffective, to $35,000, which would be considered highly cost-effective.

Credentialing for Surgeon Participation

There is no doubt that surgeon experience influences the efficacy of the procedure. In this regard, there is assurance that at least the steep part of the learning curve will not be included in the laparoscopic trial, since surgeons undergo a credentialing process prior to participation. Surgeons are considered for participation if they have performed at least 20 documented laparoscopic colorectal procedures. To insure that the cancer resections are uniform with respect to critical portions of the operation, potential investigators are also required to submit a video demonstrating their laparoscopic colon cancer techniques. Videorecording laparoscopic procedures provides a unique opportunity for not only evaluating surgeons for participation, but also for performing ongoing audit evaluations.

At present, 40 institutions throughout the United States and Canada are participating in the trial. Each surgeon is a member of the surgical consortium COST Study Group. Each surgeon is also a member of one of the large cooperative oncology groups, specifically Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group (NCCTG), National Cancer Institute of Canada (NCIC), National Surgical Adjuvant Breast and Bowel Group (NSABP), Radiation Therapy Oncology Group (RTOG) or South Western Oncology Group (SWOG).

PRELIMINARY RESULTS

At present, 408 patients have been entered into the study (Table IV). The accrual pace is keeping on schedule. Although any comparisons in terms of survival or recurrence are still premature, useful data regarding indirect parameters of adequate resection have already been reviewed. Total bowel length, proximal and distal margins, mesenteric length, and number of lymph nodes retrieved are similar between the two techniques and are consistent with the results from the retrospective studies mentioned above. Interim analysis and confidential reviews by a National Cancer Institute (NCI) Data Monitoring Committee, as is standard for large cooperative group trials, are underway.

TABLE IV. Current Accrual From the NIH Prospective Randomized Trial*

	No. patients analyzed	Open	Laparoscopic
Total No. patients accrued	408	203	205
Mean age (years)		69	67
Gender (% females)		52	48
ASA I/II (%)		87	87
ASA III (%)		13	13
Procedures performed	305	151	154
Right colectomy		77	83
Left colectomy		8	10
Sigmoid colectomy		60	57
Other		6	4
Stage distribution	305	151	154
Stage 0		10	5
Stage I		40	58
Stage II		57	45
Stage III		39	42
Stave IV		5	4
Patients with known previous abdominal surgery		53/151	60/154

*More details available at **http://ncctg.mayo.edu/lapcolon**

International Trials

Increasing interest in the treatment of colon cancer with laparoscopy has prompted several investigators around the world to start trials on laparoscopic resection for colorectal cancer, following the example of the NCI-sponsored trial (Table V). Many of these trials, in fact, share the same aims as the NCI trial: cancer outcome, safety, quality of life, and cost analysis. In some cases, international trials have been modeled on the NCI trial in an attempt to obtain comparable data, which could be subsequently pooled and result in a more powerful meta-analysis. In some cases, indications for eligibility have been expanded to include stage IV disease, transverse colon and rectal cancers. Increased eligibility criteria allow more rapid patient accrual, but at the expense of statistical power due to inhomogeneous populations. Nevertheless, that so many trials have been initiated speaks to the degree of enthusiasm about this innovative technique and the fact that there is a strong interest in defining its true potential.

Furthermore, additional investigative issues have been proposed. In some cases, trials will also be focused on specific technical complications, i.e., those specifically related to the use of a pneumoperitoneum. Others are investigating factors that could predict conversion. A Northern European study will investigate the immune status of patients to determine if an association between immunologic response and survival can be detected. In particular, serial postoperative levels of IL-1β, tumor ne-

TABLE V. International Trials Investigating Laparoscopic Colorectal Surgery for Cancer

Country	Principal investigator	Start date	Sites of resection	No. patients (expected)	Date of first analysis (expected)
New Zealand	P. Bagshaw	1998	Colon	1,260	—
The Netherlands	H.J. Bonjer	1997	Colon	1,500	2000
Great Britain	P.J. Guillou	1996	Colon and rectum	1,000	1999
Germany	F. Kockerling	1995	Colon and rectum	1,200	2000
Brazil	J.S. Souza	1993	Colon and rectum	800	1998
Spain	A.M. Lacy	1993	Colon	250	—

crosis factor α (TNFα), insulin-like growth factor 1 (IGF-1), IL-6, CRP, and albumin will be studied. Some trials will analyze circumferential and mesenteric margins, which have been shown to be independent factors predictive of local recurrence and survival in rectal cancer [52]. This will enable the investigators to establish whether laparoscopic dissection of the rectum can attain clear radial margins the same as with the open technique.

EVOLVING PERSPECTIVES IN LAPAROSCOPIC SURGERY

Innovations in Clinical Practice

As increasing data regarding laparoscopic colon surgery become available, public opinion is gradually evolving. General skepticism has been replaced by cautious enthusiasm. In part these changes reflect the evolution of laparoscopy in general. There is no doubt that equipment and instrumentation have improved over the last decade. Not only are reusable instruments more widely available, but they also have been become designed for specific applications, such as bowel manipulation. In addition, there has been a focus on improving and simplifying techniques and reducing the number of instruments, monitors, and assistants required, i.e., attempts to streamline the procedure. Increasing indications of laparoscopy for other organ removal such as splenectomy, adrenalectomy, and appendectomy have increased the overall laparoscopic experience of surgeons and the lay knowledge about, and therefore demand for, minimally invasive procedures.

There is no doubt that trends in laparoscopic general surgery translate into trends in laparoscopic colorectal surgery. Once through the learning experience, most surgeons find a reasonable reward for the effort. In a given practice, it has been possible to reduce the average narcotic requirements by 50%, LOS by 3.1 days, and hospital charges by thousands of dollars. There is no doubt this is attractive to patients and to non-surgeon-treating physicians.

Learning Curve

Despite increasing popularity, laparoscopic removal of the colon remains a technical challenge; in fact, there is little doubt that the difficulty of the procedure is in part responsible for its slow acceptance. In that regard, to predict whether the procedure will fulfill the expectations of its advocates it is necessary to understand the learning curve for laparoscopic colon surgery.

The learning curve is most typically described within the context of operative times, rates of conversion, and rates of complications. Reviewing how these three parameters change according to experience has revealed several important points about the learning curve for laparoscopic colon surgery. First, it is evident from the variable slopes of learning curve and variable ‘‘breakpoints’’ in operation times (Table VI) [5,36,56,60,62,74,75] and conversion rates (Table VII) [5,12,36,62,65] that not all surgeons operate at the same time, nor start with the same level of experience. It is likely e.g., that surgeons experienced in laparoscopic cholecystectomy and appendectomy more quickly adapt to laparoscopic colon surgery due to familiarity with general laparoscopic techniques. Factors other than the surgeons’ experience, such as the experience of other members of the operating team, and the availability of proper instrumentation specific for bowel resection, influence the learning curve. These factors likely influence the early or steep part of the learning curve. Furthermore, there is a suggestion from the data that in addition to a steep early learning experience, there is also a more gradual learning process that occurs after the first ‘‘breakpoint’’; this curve is probably related to gradual changes in technical proficiency.

Finally, it must be said that drawing firm conclusions regarding how long it takes to learn laparoscopic colon surgery is rendered more difficult due to the heterogeneity of the procedures under review. The complexity of laparoscopic bowel surgery varies according to the location and extent of bowel resected. It has been shown repeatedly that laparoscopic sigmoid resection is more challenging than laparoscopic right colectomy. In addition, segmental colon resections have met with more success than total colon resections [53]. The selection of patients ideally suited or not suited for laparoscopic surgery can influence parameters that are measured as the ‘‘learning curve.’’ Hence, all of these variables must be considered when data on operation times, conversion

TABLE VI. Effect of the Learning Curve on Operation Times for Laparoscopic Colorectal Procedures*

Reference	Year	No. patients	Type of operation	Average time (min) Early	Average time (min) Late	Time reduction (%)	Breakpoint (No. cases)
Hoffman et al. [5]	1994	80	Colon and rectal	258	185	28	40
Jansen [74]	1994	19	Rectosigmoidectomy	294	186	37	5
Van Ye et al. [56]	1994	14	Colon and rectal	348	160	54	2
Simons et al. [75][a]	1995	144	Right, left, and sigmoid colectomy	160	130	19	11–15
Wishner et al. [36]	1995	150	Colon and rectal	250	140	44	35–50
Stitz and Lumley [62]	1996	40	Right colectomy	180	130	28	20
		40	Anterior resection	240	150	38	20
Agachan et al. [60]	1997	175	Colon and rectal	201	141	30	70

*No homogeneous criteria applied.
[a]Derived from their figure 1.

TABLE VII. Effect of Learning Curve on Rates of Conversion From Laparoscopic to Open Colorectal Surgery

Reference	Year	No. patients	Early (%)	Late (%)	Breakpoint (No. cases)
Hoffman et al. [5]	1994	80	30	15	40
Senagore et al. [65]	1995	60	20	10	20
Wishner et al. [36]	1995	150	30	20	50
Lord et al. [12]	1996	55	32	8	—[a]
Stitz and Lumley [62]	1996	320	10	5	100

[a]Report describes breakpoint as last 6 months of study.

rates, and complication rates are described in relation to surgeon experience.

Operation Times

Although surgical proficiency cannot be reduced to a single parameter, it is most often estimated using operation times. Early experiences with laparoscopic colon surgery demonstrate operation times that have varied from as low as 160 min to 348 min. With experience, most surgeons find that their operation times can be reduced to within 190 min (Table VI) [54,55,59]. ''Breakpoints'' are variably reported as occurring between 2 and 70 cases. It is clear that laparoscopic cases take longer than open cases, although the differences are modest, at only 7–55 min [4–8,13,26,54,56].

There is evidence that differences in open vs. laparoscopic operation times can become minimal after a variable number of cases. In the study by Van Ye and colleagues [56], the total average time for laparoscopy was 190 min compared with 150 min for open procedures, but was reduced to 160 min after excluding the first 2 cases. In a larger series on 80 laparoscopic colorectal procedures compared to 53 open colectomies, the overall average resulted in 221 vs. 183 min but the time required for laparoscopy was decreased to 185 min when considering only the last 40 cases [5]. Assuming that different procedures are associated with varying degrees of difficulty, it is not surprising that operation times can be similar when comparing specific procedures. In a study comparing 102 laparoscopic colorectal procedures and 705 historical open controls, laparoscopic ileocolic resection and left colectomy had similar operation times (150 min for laparoscopic ileocolic resection vs. 144 min for open technique and 204 vs. 209 min for laparoscopic and open left colectomy, respectively), while the operation times for rectal resection were more notably different (288 vs. 166 min) [10]. Since increased operation times adversely influence costs, it is logical that these differences between open and laparoscopic cases must be minimized in order to realize the cost benefits of reduced LOS.

In addition to studying differences between open and laparoscopic completed cases, several authors have reported on operation times for converted cases. Interestingly, some report that converted cases typically take longer, while others report that they are shorter. In a series comparing 33 converted patients with 62 completed laparoscopic colectomies and 103 open cases, the converted cases required less operation time than the laparoscopic procedures [54]. These differences probably reflect differences in practices with respect to when laparoscopic cases are converted. That is, depends on how liberal the surgeon is in his/her decision to convert. A policy of rapid conversion will reduce the operation times and the frustrations of laparoscopic surgery. This is reasonable unless it is also associated with a high rate of conversion. No doubt the frequent conversion of cases from laparoscopic to open diminishes the gains for patients and reduces any chance of gain in terms of cost benefits, since the costs of laparoscopic instruments are not balanced by reduced LOS.

Conversion Rate

Again as stated above, surgical proficiency and the ability to learn this new procedure cannot be measured as a single variable; as such, an equally important factor is the rate of conversion.

In fact, the trend for conversion rates is similar to the trend for operation times: i.e., they improve with more

experience (Table VII). Differences detectable in early conversion rates reflect the high variability encountered in the literature, where overall conversion rates range from a low of 2% [10] to a high of 41% [2]. Several other series from both the United States and Europe have reported rates below 10% [9,34,57–59], with rates of 20% generally considered acceptable. In addition, the percent reduction and the number of cases required as a ''breakpoint'' range from 5% in 100 cases to 24% reduction with a total of 55 patients.

Although it is tempting to believe that improvements in conversion rates reflect improvements in surgical proficiency, this may represent an oversimplification. In fact, several authors have documented a number of variables influencing the need for conversion, including patient- and disease-related factors as well as surgical experience and philosophy. When patient selection criteria are kept stable, conversion rates tend to decrease as a result of increased proficiency. However, since it is not uncommon for experienced surgeons to liberalize the indications for laparoscopic surgery, in other words, take on more difficult and challenging cases, conversion rates may remain stable, while the degree of difficulty increases [31,60]. The threshold for conversion is also influenced by a surgeon's experience and philosophy. Each surgeon must find a level of comfort with laparoscopic surgery, and safety issues should always take priority.

The tendency to convert to open surgery is clearly influenced by a number of patient- and disease-related factors. Although there are only a few absolute contraindications to surgery, including severe coagulopathy, cardiac, respiratory, or liver disease, as well as symptoms of complex and advanced local disease, such as obstruction or contained perforation [61], there are a number of relative contraindications to laparoscopic surgery, or conditions capable of portending a high rate of conversion. Obesity—a weight in excess of 90 kg—has been associated with conversion rates as high as 75% in a series of 122 patients [30]. Since this was an early report prior to the introduction of longer instruments, this rate may have declined in recent years. Another relative contraindication is the presence of dense adhesions. Although conversion rates have been reported to be higher in patients with previous abdominal surgery, one has to take into consideration the site of the previous surgery vs. the planned surgery. For example, a previous appendectomy or cholecystectomy may increase the chance of adhesions in the right abdomen, rendering right colectomy difficult. Similarly, the location of the site of resection is also important [2,5,62]. Right colon resection is more likely to be completed laparoscopically than left colon, sigmoid, and rectal resections [54]. In a multicenter study by the American Society of Colon and Rectal Surgery (ASCRS), including 114 different surgeons, the overall conversion rate was 22.8%. While rectal cases accounted for 33.5%, right hemicolectomies were associated with a conversion rate of 16% [63]. Finally, the conversion rates are likely disease-specific. Although not clearly defined, at least the presence of Hinchey stage 2 diverticulitis can be associated with conversion rates of up to 50% [64].

In summary, whether rates of conversion decrease or not is heavily influenced by several factors, including patient and disease selection and surgical experience and proficiency. Nevertheless, these data provide some assurance that with increasing experience, acceptable rates of conversion can be accomplished. This is key to maximizing the benefits of laparoscopic surgery without adversely affecting the costs.

Complication Rates

A relatively unreported parameter associated with a learning curve is the incidence of postoperative complications. Several authors have reported a gradual reduction in complication rates along with experience [38,55,65]. In the same multicenter series on 1,194 patients as mentioned above, the postoperative complication rates were 17.3% for surgeons who had performed between 1 and 29 cases, 22.5% if 30–39 cases had been carried out, and 9.8% when the experience had reached at least 39 cases. Separate multivariate analysis has revealed that the same trend continued also beyond 40 cases; i.e., the complication rate kept declining as the experience of the individual surgeon increased [63]. There is also evidence from a more detailed analysis of specific complications that increased experience can lead to a reduction of laparoscopy-related complications. In a series of 195 patients, a comparison between early and late experience was associated with a reduction from 13.8% to 2.8% [31]. These results confirm that laparoscopic technique is not associated per se with an increased complication rate and can become safe and comparable to open technique when sufficient familiarity is acquired.

A better understanding of the various aspects of the learning curve carries a significant influence on its applicability. At this stage, several authors have gained sufficient experience and familiarity with the technique and have clearly shown that it can be applied on a wide-scale basis after an adequate learning period. Also, as more and more surgeons are trained to become adept at laparoscopic surgery in multiple areas, such as gallbladder, appendix, hernias, spleen, etc., then the more natural it will be for them to take out more complex organs, such as the colon. The primary issue concerns the volume of laparoscopy surgery that is performed and the degree of experience that is gained, both from training programs and from practice. Acknowledging differing degrees of difficulty for laparoscopic cases, some investigators have proposed an orderly sequence of learning steps to gain

confidence with increasingly more elaborate procedures [66].

CONCLUSIONS

Laparoscopic colectomy has repeatedly been demonstrated to be feasible, safe, and reasonable. Patient-related benefits can be realized and satisfy an increasing demand. Indications for laparoscopic colorectal surgery are expanding and more difficult procedures are being introduced gradually into daily practice. Several clinical trials are currently underway to evaluate the benefits and the potential risks of the technique as a cancer operation. Meanwhile, oncologic issues are still unresolved and controlled trials are advised prior to widespread acceptance. Four trials will have completed accrual and three will be able to offer early analysis of the results by the year 2001.

REFERENCES

1. Ortega AE, Beart RW Jr, Steele GD Jr, et al.: Laparoscopic Bowel Surgery Registry. Preliminary results. Dis Colon Rectum 1995;38:681–685.
2. Falk PM, Beart RW Jr, Wexner SD, et al.: Laparoscopic colectomy: A critical appraisal. Dis Colon Rectum 1993;36:28–34.
3. Peters WR, Bartels TL: Minimally invasive colectomy: Are the potential benefits realized? Dis Colon Rectum 1993;36:751–756.
4. Senagore AJ, Luchtefeld MA, Mackeigan JM, et al.: Open colectomy versus laparoscopic colectomy: Are there differences? Am Surg 1993;59:549–553.
5. Hoffman GC, Baker JW, Fitchett CW, et al.: Laparoscopic-assisted colectomy. Initial experience. Ann Surg 1994;219:732–740.
6. Musser DJ, Boorse RC, Madera F, et al.: Laparoscopic colectomy: At what cost? Surg Laparosc Endosc 1994;4:1–5.
7. Lacy AM, Garcia-Valdecasas JC, Pique JM, et al.: Short-term outcome analysis of a randomized study comparing laparoscopic vs. open colectomy for colon cancer. Surg Endosc 1995;9:1101–1105.
8. Saba AK, Kerlakian GM, Kasper GC, et al.: Laparoscopic assisted colectomies versus open colectomy. J Laparosc Surg 1995;5:1–6.
9. Franklin ME Jr, Rosenthal D, Abrego-Medina D, et al.: Prospective comparison of open vs. laparoscopic colon surgery for carcinoma. Five-year results. Dis Colon Rectum 1996;39:S35–46.
10. Gellmann L, Salky B, Edye M: Laparoscopic assisted colectomy. Surg Endosc 1996;10:1041–1044.
11. Liberman MA, Phillips EH, Carroll BJ, et al.: Laparoscopic colectomy vs. traditional colectomy for diverticulitis. Outcome and costs. Surg Endosc 1996;10:15–18.
12. Lord SA, Larach SW, Ferrara A, et al.: Laparoscopic resections for colorectal carcinoma. A three-year experience. Dis Colon Rectum 1996;39:148–154.
13. Leung KL, Kwok SP, Lau WY, et al.: Laparoscpic-assisted resection of rectosigmoid carcinoma. Immediate and medium-term results. Arch Surg 1997;132:761–764.
14. Disbrow EA, Bennett HL, Owings JT: Effect of preoperative suggestion on postoperative gastrointestinal motility. West J Med 1993;158:488–492.
15. Bohm B, Milsom JW, Fazio VW: Postoperative intestinal motility following conventional and laparoscopic intestinal surgery. Arch Surg 1995;130:415–419.
16. Hotokezaka M, Combs MJ, Schirmer BD: Recovery of gastrointestinal motility following open versus laparoscopic colon resection in dogs. Dig Dis Sci 1996;41:705–710.
17. Bessler M, Whelan RL, Halverson A, et al.: Controlled trial of laparoscopic-assisted vs. open colon resection in a porcine model. Surg Endosc 1996;10:732–735.
18. Davies W, Kollmorgen CF, Tu QM, et al.: Laparoscopic colectomy shortens postoperative ileus in a canine model. Surgery 1997;121:550–555.
19. Reissman P, Teoh TA, Cohen SM, et al.: Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. Ann Surg 1995;222:73–77.
20. Fleshman JW, Fry RD, Birnbaum EH, et al.: Laparoscopic-assisted and minilaparotomy approaches to colorectal diseases are similar in early outcome. Dis Colon Rectum 1996;39:15–22.
21. Hartsell PA, Frazee RC, Harrison JB, et al.: Early postoperative feeding after elective colorectal surgery. Arch Surg 1997;132:518–520.
22. Pfeifer J, Wexner SD, Reissman P, et al.: Laparoscopic vs. open colon surgery. Costs and outcome. Surg Endosc 1995;9:1322–1326.
23. Frazee RC, Roberts JW, Okeson GC, et al.: Open versus laparoscopic cholecystectomy. A comparison of postoperative pulmonary function. Ann Surg 1991;213:651–653.
24. Harmon GD, Senagore AJ, Kilbride MJ, et al.: Interleukin-6 response to laparoscopic and open colectomy. Dis Colon Rectum 1994;37:754–759.
25. Allendorf JD, Bessler M, Whelan RL, et al.: Postoperative immune function varies inversely with the degree of surgical trauma in a murine model. Surg Endosc 1997;11:427–430.
26. Stage JG, Schulze S, Moller P, et al.: Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. Br J Surg 1997;84:391–396.
27. Fukushima R, Kawamura YJ, Saito H, et al.: Interleukin-6 and stress hormone responses after uncomplicated gasless laparoscopic-assisted and open sigmoid colectomy. Dis Colon Rectum 1996;39:S29–34.
28. Franklin ME Jr, Rosenthal D, Norem RF: Prospective evaluation of laparoscopic colon resection versus open colon resection for adenocarcinoma. A multicenter study. Surg Endosc 1995;9:811–816.
29. Lumley JW, Fielding GA, Rhodes M, et al.: Laparoscopic-assisted colorectal surgery. Lessons learned from 240 consecutive patients. Dis Colon Rectum 1996;39:155–159.
30. Dean PA, Beart RW Jr, Nelson H, et al.: Laparoscopic-assisted segmental colectomy: Early Mayo Clinic experience. Mayo Clin Proc 1994;69:834–840.
31. Larach SW, Patankar SK, Ferrara A, et al.: Complications of laparoscopic colorectal surgery. Analysis and comparison of early vs. latter experience. Dis Colon Rectum 1997;40:592–596.
32. Guillou PJ, Darzi A, Monson JR: Experience with laparoscopic colorectal surgery for malignant disease. Surg Oncol 1993;2(Suppl 1):43–49.
33. Puente I, Sosa JL, Sleeman D, et al.: Laparoscopic assisted colorectal surgery. J Laparosc Surg 1994;4:1–7.
34. Zucker KA, Pitcher DE, Martin DT, et al.: Laparoscopic-assisted colon resection. Surg Endosc 1994;8:12–17.
35. Tucker JG, Ambroze WL, Orangio GR, et al.: Laparoscopically assisted bowel surgery. Analysis of 114 cases. Surg Endosc 1995;9:297–300.
36. Wishner JD, Baker JW, Jr, Hoffman GC, et al.: Laparoscopic-assisted colectomy. The learning curve. Surg Endosc 1995;9:1179–1183.
37. Kwok SP, Lau WY, Carey PD, et al.: Prospective evaluation of laparoscopic-assisted large bowel excision for cancer. Ann Surg 1996;223:170–176.
38. Fielding GA, Lumley J, Nathanson L, et al.: Laparoscopic colectomy. Surg Endosc 1997;11:745–749.
39. De Wilde RL: Goodbye to late bowel obstruction after appendicectomy. Lancet 1991;338:1012.
40. Monson JR, Darzi A, Carey PD, et al.: Prospective evaluation of laparoscopic-assisted colectomy in an unselected group of patients. Lancet 1992;340:831–833.
41. Nduka CC, Monson JR, Menzies-Gow N, et al.: Abdominal wall metastases following laparoscopy. Br J Surg 1994;81:648–652.
42. Berends FJ, Kazemier G, Bonjer HJ, et al.: Subcutaneous metastases after laparoscopic colectomy. Lancet 1994;344:58.
43. Reilly WT, Nelson H, Schroder G, et al.: Wound recurrence following conventional treatment of colorectal cancer. A rare but

perhaps underestimated problem. Dis Colon Rectum 1996;39:200–207.
44. Hughes ES, McDermott FT, Polglase AL, et al.: Tumor recurrence in the abdominal wall scar tissue after large-bowel cancer surgery. Dis Colon Rectum 1983;26:571–572.
45. Cass AW, Million RR, Pfaff WW: Patterns of recurrence following surgery alone for adenocarcinoma of the colon and rectum. Cancer 1976;37:2861–2865.
46. Leather AJ, Kocjan G, Savage F, et al.: Detection of free malignant cells in the peritoneal cavity before and after resection of colorectal cancer. Dis Colon Rectum 1994;37:814–819.
47. Hewett PJ, Thomas WM, King G, et al.: Intraperitoneal cell movement during abdominal carbon dioxide insufflation and laparoscopy. An in vivo model. Dis Colon Rectum 1996;39:S62–66.
48. Fleshman JW, Nelson H, Peters WR, et al.; Early results of laparoscopic surgery for colorectal cancer. Retrospective analysis of 372 patients treated by Clinical Outcomes of Surgical Therapy (COST) Study Group. Dis Colon Rectum 1996;39:S53–58.
49. Johnstone PA, Rohde DC, Swartz SE, et al.: Port site recurrences after laparoscopic and thoracoscopic procedures in malignancy. J Clin Oncol 1996;14:1950–1956.
50. Nelson H, Weeks JC, Wieand HS: Proposed phase III trial comparing laparoscopic-assisted colectomy versus open colectomy for colon cancer. J Natl Cancer Inst 1994;19:51–56.
51. Keats AS: The ASA classification of physical status—A recapitulation. Anesthesiology 1978;49:233–236.
52. Adam IJ, Mohamdee MO, Martin IG, et al.: Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994;344:707–711.
53. Schmitt SL, Cohen SM, Wexner SD, et al.: Does laparoscopic-assisted ileal pouch anal anastomosis reduce the length of hospitalization? Int J Colorect Dis 1994;9:134–137.
54. Ramos JM, Beart RW Jr, Goes R, et al.: Role of laparoscopy in colorectal surgery. A prospective evaluation of 200 cases. Dis Colon Rectum 1995;38:494–501.
55. Fowler DL, White SA, Anderson CA: Laparoscopic colon resection: 60 cases. Surg Laparosc Endosc 1995;5:468–471.
56. Van Ye TM, Cattey RP, Henry LG: Laparoscopically assisted colon resections compare favorably with open technique. Surg Laparosc Endosc 1994;4:25–31.
57. Wexner SD, Cohen SM, Johansen OB, et al.: Laparoscopic colorectal surgery: A prospective assessment and current perspective. Br J Surg 1993;80:1602–1605.
58. Boulez J: Chirurgie du cancer colorectal par voie coelioscopique. Ann Chir 1996;50:219–230 (in French).
59. Kockerling F, Schneider C, Reymond MA, et al., and Laparoscopic Colorectal Surgery Study Group (LCSSG): Early results of a prospective multicenter study on 500 consecutive cases of laparoscopic colorectal surgery. Surg Endosc 1998;12:37–41.
60. Agachan F, Joo JS, Sher M, et al.: Laparoscopic colorectal surgery. Do we get faster? Surg Endosc 1997;11:331–335.
61. Elftmann TD, Nelson H, Ota DM, et al., Laparoscopic-assisted segmental colectomy: Surgical techniques. Mayo Clin Proc 1994;69:825–833.
62. Stitz RW, Lumley JW: Laparoscopic colorectal surgery—New advances and techniques. Ann Acad Med Sing 1996;25:653–656.
63. Bennett CL, Stryker SJ, Ferreira MR, et al.: The learning curve for laparoscopic colorectal surgery. Preliminary results from a prospective analysis of 1,194 laparoscopic-assisted colectomies. Arch Surg 1997;132:41–44.
64. Sher ME, Agachan F, Bortul M, et al.: Laparoscopic surgery for diverticulitis. Surg Endosc 1997;11:264–267.
65. Senagore AJ, Luchtefeld MA, Mackeigan JM: What is the learning curve for laparoscopic colectomy? Am Surg 1995;61:681–685.
66. Geis WP, Coletta AV, Verdeja JC, et al.: Sequential psychomotor skills development in laparoscopic colon surgery. Arch Surg 1994;129:206–212.
67. Fine AP, Lanasa S, Gannon MP, et al.: Laparoscopic colon surgery: Report of a series. Am Surg 1995;61:412–416.
68. Philipson BM, Bokey EL, Moore JW, et al.: Cost of open versus laparoscopically assisted right hemicolectomy for cancer. World J Surg 1997;21:214–217.
69. Moore JW, Bokey EL, Newland RC, et al.: Lymphovascular clearance in laparoscopically assisted right hemicolectomy is similar to open surgery. Aust NZ J Surg 1996;66:605–607.
70. Drouard F, Passone-Szerzyna N: Les greffes neoplasiques parietales en chirurgie laparoscypique colo-rectale. Commun III Symp SFCE Bordeaux 1995 (in French).
71. Hoffman GC, Baker JW, Doxey JB, et al.: Minimally invasive surgery for colorectal cancer. Initial follow-up. Ann Surg 1996;223:790–796.
72. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al.: Postoperative complications of laparoscopic-assisted colectomy. Surg Endosc 1997;11:119–122.
73. Vukasin P, Ortega AE, Greene FL, et al.: Wound recurrence following laparoscopic colon cancer resection. Results of the American Society of Colon and Rectal Surgeons Laparoscopic Registry. Dis Colon Rectum 1996;39:S20–23.
74. Jansen A: Laparoscopic-assisted colon resection. Evolution from an experimental technique to a standardized surgical procedure. Ann Chir Gynecol 1994;83:86–91.
75. Simons AJ, Anthone GJ, Ortega AE, et al.: Laparoscopic-assisted colectomy learning curve. Dis Colon Rectum 1995;38:600–603.